PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 June 1999 (04.06.99)	
International application No. PCT/GB98/03076	**Applicant's or agent's file reference** 1591
International filing date (day/month/year) 12 October 1998 (12.10.98)	**Priority date** (day/month/year) 15 October 1997 (15.10.97)
Applicant IVERSEN, Leslie, Lars	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

20 April 1999 (20.04.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

S. Mafla

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

11591 F. Docs

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SANDERSON Laurence A.
SANDERSON & CO.
34 East Stockwell Street
Colchester
Essex CO1 1ST
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	03. 07. 00
Applicant's or agent's file reference 7/11591	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/03076	12/10/1998	15/10/1997

Applicant
PANOS THERAPEUTICS LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	THORNTON, J Tel.+49 89 2399-8072

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
7/11591		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB98/03076	12/10/1998	15/10/1997
International Patent Classification (IPC) or national classification and IPC A61K31/55		
Applicant PANOS THERAPEUTICS LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/04/1999	23.05.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Heller, D Telephone No. +49 89 2399 8746

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/03076

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

   Description, pages:

   1-11 as originally filed

   Claims, No.:

   1-20 as originally filed

2. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 17-20.

because:

☒ the said international application, or the said claims Nos. 17-20 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	see sections III and V
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section III:

Claims 17 to 20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V:

Prior art

Reference is made to the following documents:
D1: US-A-4 791 215
D2: GB-A-1 564 039
D3: EP-A-0 222 614
D4: EP-A-0 391 369

Novelty

The subject-matter of claims 1 to 20 is new in the sense of Article 33 (2) PCT.

D1 describes derivatives of D,L-glutamic acid and D,L-aspartic acid that have antagonistic activity toward exogenous or endogenous bioactive polypeptides (col. 1, lines 6 to 9). The compounds have an antagonistic activity towards bioactive polypeptides and are useful particularly in the treatment of illnesses of the digestive system and the central nervous system, as pain killers, and for the treatment of anorexia and those affections in which exogenous or endogenous bioactive polypeptides are involved (col. 1, lines 38 to 45). The invention further includes the administration of morphine after the administration of said compounds (col. 11, lines 42 to 46).
As D1 does not describe a formulation, which contains both - the CCK antagonist and the opioid -, it does not anticipate novelty of present claims 1 to 20. Further, D1 lacks the biphasic carrier.

D2 discloses an analgesic composition comprising propoxyphene or a pharmaceutically acceptable salt and at least one benzodiazepine or a pharmaceutically accepted salt (claim 1).
D2 differs from the present invention in the biphasic carrier and does not anticipate novelty of present claims 1 to 20.

D3 is directed to a pharmaceutical formulation in capsule unit dosage form comprising a gelatin capsule containing a semi-solid matrix, said semi-solid matrix comprising an antibacterial agent, a pharmaceutically acceptable hydrophobic carrier matrix and a hydrophilic substance (page 2, lines 47 to 52) capable of creating channels in the hydrophobic carrier matrix (page 2, line 62 to page 3, line 14) thereby providing a sustained rate of release of the active agent from the formulation (claim 1).
The hydrophobic carrier matrices employed herein are amphiphiles in which the molecule or ion contains both hydrophilic and lipophilic portions (page 3, lines 1 to 3) and include the glycerides and partial glycerides (page 3, lines 9 and 10).
As D3 only describes a biphasic carrier similar to that of the present application, but is silent to any substance of the present claims 1 to 20, it does not anticipate novelty of said claims.

D4 relates to pharmaceutical compositions of hydrophobic drugs being in the form of an oil-in-water emulsion. The pharmaceutical compositions provided by the present invention show an outstanding long term stability and, in addition, in various forms of administration they also have sustained release characteristics (page 1, lines 1 to 3).
Example 2 in D4 discloses a oil-in-water emulsion containing diazepam (page 8).
Further, several lipophilic drugs, including benzodiazepines and morphine can be administered in such an oil-in-water emulsion (claims 21 to 25).
D4 does not contain the same combination of substances as claim 1. Therefore, present claims 1 to 20 are novel over D4 according to Article 33 (3) PCT.

Inventive Step

The subject-matter of claims 1 to 20 does not involve an inventive step in the sense of Article 33 (3) PCT.

As D2 already discloses an analgesic composition comprising as analgesically active

compounds propoxyphene related structurally to methadone (= opioid) (col. 1, line 16) and at least one benzodiazepine in an amount which potentiates the analgesic activity of the propoxyphene (claim 1), D2 which is the closest prior art differs from the present invention only in that it does not contain the biphasic carrier. The CCK antagonist of present invention includes also benzodiazepines (claim 14), which already potentiate the analgesic activity of the opioid in D2. The pharmacological mechanism - which may be different in D2 - is not relevant for present claim 1.

The problem to be solved can be described as how to provide further formulations facilitating a co-administration of a CCK antagonist and an opioid.

D3 and D4 do not describe such combinations of substances according to claim 1, but they contain formulations with biphasic carriers as claimed in claim 1. It seems that the use of such biphasic carriers is well-known. Therefore, it is obvious for a person skilled in the art to combine the teaching of D2 with the teaching of D3 or D4 to solve the above-mentioned problem. With respect to the teaching D4, it would be obvious for a person skilled in the art to include a hydrophilic drug in the water phase of the emulsion like the hydrophobic drug in the oil phase.
Further, no surprising aspect of a formulation according to the application as filed is described.
Therefore, present claims 1 to 20 are not inventive according to the prior art as described above (Article 33 (3) PCT).

Industrial applicability

For the assessment of the present claims 17 to 20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VIII

The formulas in the description on page 6 are unclear as the substituents are not identified. This implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

FORMAL DOCUMENTS
SECTION 115 ENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
SANDERSON & CO.
34 East Stockwell Street
Colchester
Essex CO1 1ST
UNITED KINGDOM

Date of mailing *(day/month/year)* 16/02/1999	
Applicant's or agent's file reference 1591	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/GB 98/03076	International filing date *(day/month/year)* 12/10/1998

Applicant

PANOS THERAPEUTICS LIMITED et al.

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicants's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Barbara Klaver

Form PCT/ISA/220 (January 1994)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
1591		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 98/03076	12/10/1998	15/10/1997

Applicant

PANOS THERAPEUTICS LIMITED et al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant
   - [X] the text has been established by this Authority to read as follows:

   ANALGESIC COMPOSITIONS

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. –
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/GB 98/03076

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 20 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

[redacted]tional Application No
PCT/GB 98/03076

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/55 A61K9/107 A61K9/20 //(A61K31/55,31:485)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 791 215 A (ROVATI ET AL.) 13 December 1988 cited in the application see column 1, line 1 - line 44 see column 31, line 4 - line 45	1-20
A	GB 1 564 039 A (BERGER) 2 April 1980 see the whole document	1-20
A	EP 0 222 614 A (ELI LILLY AND COMPANY) 20 May 1987 see the whole document	1-20
A	EP 0 391 369 A (YISSUM RES. DEV. COMP. HEBREW UNIVERS. JERUSALEM) 10 October 1990 see page 8; example 2	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 February 1999	16/02/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/03076

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 4791215	A	13-12-1988	AT	390949 B	25-07-1990
			AT	186985 A	15-01-1990
			AU	566601 B	22-10-1987
			AU	4410985 A	02-01-1986
			BE	902726 A	16-10-1985
			CA	1325633 A	28-12-1993
			CH	674203 A	15-05-1990
			DE	3522506 A	02-01-1986
			DK	285685 A	26-12-1985
			FR	2566397 A	27-12-1985
			GB	2160869 A,B	02-01-1986
			IE	57892 B	05-05-1993
			JP	1784500 C	31-08-1993
			JP	4073425 B	20-11-1992
			JP	61044855 A	04-03-1986
			NL	8501829 A	16-01-1986
			SE	503111 C	25-03-1996
			SE	8503097 A	26-12-1985
			PT	80692 B	19-08-1987
GB 1564039	A	02-04-1980	NONE		
EP 222614	A	20-05-1987	US	4797286 A	10-01-1989
			AU	591723 B	14-12-1989
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(57) Abstract

Pharmaceutical formulations, particularly suitable for treating chronic and neuropathic pain comprise an opioid–potentiating amount of a CCK antagonist and an analgesic amount of an opioid in a pharmaceutically acceptable biphasic carrier comprising an organic phase comprising a glyceride derivative and a hydrophilic phase.

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ANALGESIC COMPOSITIONS

The present invention relates to pharmaceutical formulations suitable for treating pain, in particular, neuropathic pain and/or dysesthesia, and their preparation. In particular, the present invention relates to formulations comprising a cholecystokinin antagonist and an opioid.

Cholecystokinin (hereinafter 'CCK') has been implicated in a variety of physiological functions, one of which is the control of pain. CCK has been shown to have a heterogeneous distribution within the brain, with the greatest levels being found in the hippocampus, cerebral cortex, amygdala and olfactory lobes. The physiological role of central CCK receptors is still under investigation, but it has many of the features of a neurotransmitter. CCK has been found in regions of the brain known to be associated with pain modulation. Furthermore, mole-per-mole, CCK has been found to be much more potent than morphine in tests for analgesia.

However, at variance with these findings, are results of tests which imply that CCK may antagonise endogenous opiate action. (Faris et al. in Science 219 310-2 (1983)). There is evidence that exogenous CCK attenuates analgesia induced by morphine or release of endogenous opioids. These disparate findings and others imply that large doses of CCK induce a 'pharmacological' analgesia whereas small doses of the peptide produce physiological antagonism of opioid analagesics.

CCK also appears to play a rôle in the development of tolerance to opioid analgesia as blockade of CCK receptors has been shown to prevent tolerance to morphine. Hence, blockade of CCK receptors by CCK antagonists may reverse or prevent the development of opiate tolerance in patients, and also potentiates the analgesic effects of opioids. The present invention is therefore based on the thesis that blockage of CCK action may be an effective supplement to morphine (or other opioid) administration in the treatment of chronic pain. However, it is believed that this opioid facilitation is preferentially mediated by the central CCK type B receptors

since CCK-B antagonists seem to potentiate the analgesic effects of both opioids and non-opioids at the spinal level. Furthermore, facilitation of opiate-induced analgesia by CCK-B receptor antagonists seem to be restricted to μ-, rather than d-, opioid receptor-mediated antinociception. Such μ-opioid againsts include morphine and hydroxymethyl fentanyl. However, potentiation of the analgesic effects produced by these opioids has also been observed with (relatively higher doses of) a CCK-A antagonist.

The present invention therefore generally relates to pharmaceutical formulations comprising an opioid-potentiating amount of a CCK antagonist together with an analgesic amount of an opioid. However, although the most popularly-used opioids such as morphine are not difficult to formulate, particularly for administration by injection, as they are water-soluble drugs, many CCK antagonists, particularly the preferred CCK antagonists to which this invention relates, are relatively insoluble compounds which are therefore pharmaceutically incompatible with hitherto-known formulations of opiate drugs. Having therefore taken the step of appreciating the advantages to be gained by co-administration of an opioid with a CCK antagonist in a single formulation, it was then realised that such a formulation, or a satisfactory carrier for the combination of active ingredients, was not available.

The present invention is therefore directed at solving this problem and provides a pharmaceutical formulation comprising

(a) an opioid-potentiating amount of a CCK antagonist;

(b) an analgesic amount of an opioid; and

(c) a pharmaceutically acceptable biphasic carrier comprising

  (i) an organic phase comprising a glyceride derivative; and

  (ii) a hydrophilic phase.

The organic phase may be either solid or liquid at room temperature but preferably has a solubilising capacity for the CCK antagonist in excess of 5mg per gram of organic phase. Examples are oils comprising a glyceride

which is liquid at room temperature and glyceride waxes having melting points in the range 35-80°C.

The organic phase may therefore comprise, for example, soya bean, safflower, sesame, rapeseed, peanut, olive, cotton seed or fish oils. Preferably, soya bean and/or safflower oils are chosen, alone or in combination with glycerine. Alternatively, the organic phase may comprise waxes such as full and/or partial glycerides of fatty acids. Preferably, such waxes are triglycerides and partial glycerides of unsaturated C_{12-18} fatty acids such as, for example, Witepsol H15 or W25.

The hydrophilic phase may itself be aqueous, or may be anhydrous but take in and/or dissolve in water in vivo. In the case of formulations for intravenous use, the hydrophilic phase preferably has a viscosity of from 2500-7500cp (2% aqueous at 20°C), more preferably around 4000cp. Such ingredients may also be added to prevent or reduce coalescence of oily droplets of the organic phase. In the case of solid formulations such as tablets and suppositories, the hydrophilic phase is gel-forming and incorporates the opioid in the gel, and also forms a matrix for incorporating the CCK antagonist plus glyceride. The hydrophilic or aqueous phase may therefore comprise a pharmacologically and pharmaceutically acceptable polymer or salts thereof which may be selected from proteins such as gelatine, hyaluronic acid, alginic acids or salts thereof such as sodium alginate, carboxymethylcellulose (optionally cross-linked), methyl cellulose, other cellulose derivatives which are water-swellable such as hydroxypropylmethyl-cellulose and hydroxyethyl cellulose or other water-swellable polymers such as polyvinyl pyrrolidone (PVP) or water-soluble polymers such as lactose.

In the formulation, the organic and hydrophilic phases may be separated or may be combined, for example, to form an oil-in-water emulsion. Preferred such emulsions therefore comprise:

(i) an oil phase comprising a glyceride derivative; and

(ii) an aqueous phase optionally comprising a buffer whereby the

emulsion has a pH of from 6.5 to 7.5 and optionally comprising an isotonicity regulator whereby the aqueous phase is made isotonic to blood plasma.

When the carrier is in the form of an emulsion, the average particle size of the resultant emulsion is preferably in the range 0.2 to 3.0μm, more preferably around 1μm.

Optionally, an emulsifying agent and/or surfactant may be incorporated into the carrier. A suitable surfactant is a sorbitan derivative such as the polysorbates, for example polysorbate 80, or sorbitan mono-oleate, and the poloxamers such as Pluronic F38. Suitable emulsifying agents include egg yolk lecithin, egg yolk phospholipids such as phosphatidyl choline and the like.

To adjust the pH, a suitable pH adjuster (i.e. an acidifying or alkalising agent) is used such as hydrochloric acid or sodium hydroxide, or a buffer such as a phosphate buffer system. Preferably, the pH is adjusted to 7-7.5, more preferably, it is close to neutral (pH = 7).

Liquid formulations may also comprise an isotonicity regulator to ensure that the aqueous phase thereof is or remains isotonic to blood plasma. Examples of such isotonicity regulators include dextrose, glucose, mannitol, sorbitol, glycerol and sodium chloride.

Other hydrophobic or hydrophilic components may be included in the formulation such as, particularly in the case of suppositories, a thickener or gelling agent for the organic phase such as hydrophobic silicon dioxide or silica; lubricants, particularly in the case of tablet formulations, such as magnesium stearate, stearic acid, talc and LUBITROL, preferably magnesium stearate. Optional other ingredients include colouring or flavouring agents, release agents, pore-forming agents, stabilisers, and fillers or diluents such as lactose, calcium phosphate or carbonate, microcrystalline cellulose and the like, and antioxidants.

Also, in the case of tablets, a coating may be applied such as waxes, fatty alcohols, water-insoluble cellulose derivatives, other water-insoluble polymers such as polymers or copolymers of acrylates and/or methacrylates

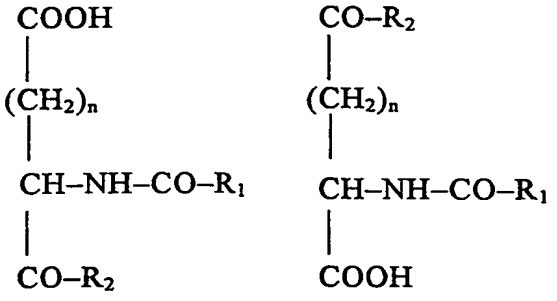
(eg. EUDRAGIT), ethylcellulose, cellulose acetate, shellac, hydrogenated vegetable oils and the like. Such a coating may provide the mechanism to enable controlled release of the opioid. Such a coating may optionally include a plasticizer or film enhancer such as monoglycerides, phthalates, sebacates, citrates, castor oil and the like.

Preferably, the CCK antagonist is incorporated into the organic phase, and more preferably into the glyceride derivative, and the opioid analgesic is incorporated into the hydrophilic phase. However, the present invention does not preclude having components (a) and (b) present in any combination in any phase of the carrier.

The components are preferably present within the following ranges of ratios: 10:1 to 1:5, respectively (i):(ii); and 1:2 to 1:40, respectively (a):(b).

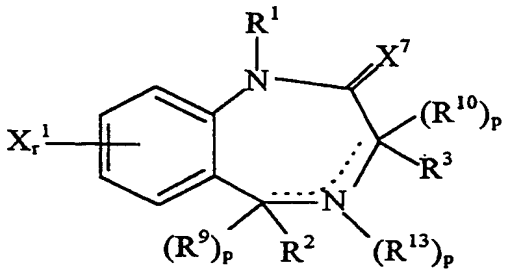
The opiate drug may be selected from those which are effective analgesics and particularly those which need to be administered at relatively high or increasing doses. Examples include morphine, or a salt thereof such as the sulphate, chloride or hydrochloride, or other 14-hydroxymorphinan opioid analgesics such as naloxone, meperidine, butorphanol or pentazocine, or morphine-6-glucuronide, codeine, dihydrocodeine, diamorphine, dextropropoxyphene, pethidine or fentanyl, or a salt of any of these.

The CCK antagonist may be selected from any of those which potentiate the analgesic effects of the opioid chosen and/or which reverse or prevent patient tolerance thereto. For example, CCK antagonists include those of formulae (I)-(IV) which are defined, respectively, in (I) US 4791 215; (II) EPs 167 919 and 284 256; (III) EP 405 537; and (IV) J. Med. Chem. 34 1508 (1991), which are herein incorporated by reference in their entirety.



(Ia)

(Ib)



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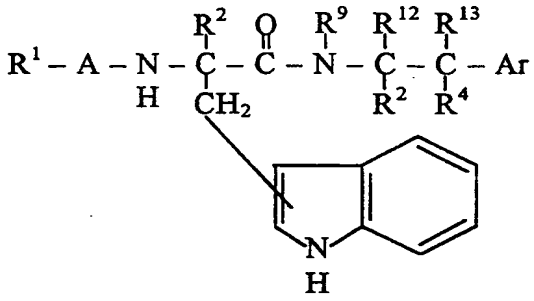

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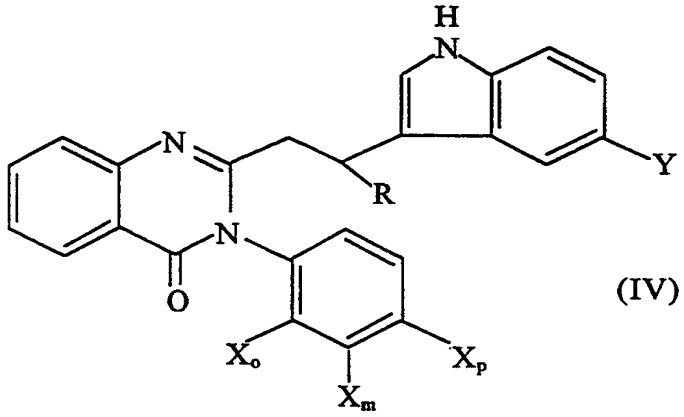

(IV)

Preferred CCK antagonists are selected from those described in European patents specifications nos. 167 919; 284 256; 508 796; 652 871; 411 668; 421 802; and 617 621, which are herein incorporated by reference in their entirety. Particularly preferred CCK antagonists include devazepide (also known as MK-329), namely, 3S-(-)-(1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (a CCK-A antagonist); L-365,260, namely 3R-3-(N'-(3-methylphenyl)ureido)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (a CCK-B

antagonist); and so-called second generation compounds such as L-369,466, namely N-[1,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzo-diazepin-3-yl]-N'-[3-(1,2,4-oxodiazol-5-one)phenyl]urea, L-741,528, namely (-)-N-[2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[indan-5-yl]urea and [N-[(3R)-5-(3-azabi-cyclo [3,2,2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-(3-methylphenyl) urea] (L-740,093, a CCK-B antagonist described in Molecular Pharmacol. 46 943-8 (1994)). Especially preferred are the CCK-B antagonists, in particular L-365,260 and the previously-mentioned second generation compounds.

The formulations of the present invention are preferably sustained-, slow- or continuous-release (S.R.) solid formulations, or emulsions for injection. S.R. formulations may be in the form of a suppository or tablet, for example.

The formulations of the present invention are particularly suitable for treating chronic and neuropathic pain. Nerve damage arising from either trauma or disease affecting peripheral nerves leads to abnormal pain states referred to as neuropathic pain. Such pain may be long-lasting and continue for extended periods after the initial injury has healed. Individuals afflicted with neuropathic pain show a marked sensitivity to nociceptive stimuli, indicative of a lowered nociceptive threshold (hyperalgesia). Moreover, there is also a perception of normally innocuous stimuli being nociceptive, a state referred to as allodynia.

In particular, these formulations are suitable for treating patients with spinal cord injury. They prevent tolerance to the opioid analgesic and eliminate the need to increase doses of opioid to clinically unacceptable levels. However, they are also useful in enhancing opioid analgesia in non-pathological pain states, and the anxiolytic (anti-anxiety or anti-panic) effects of some CCK antagonists is a particularly beneficial additional effect.

A suitable daily dose or CCK antagonist in these formulations would preferably be in the range 0.5 to 300mg per day, such as 1 to 100mg/day

(oral or via suppository) or 1 to 300mg/day (i.v.). Preferably, for MK-329, the dose would be 1-10mg/day (5-10 mg/day orally or 1-3mg/day i.v.); for L-365,260, the dose would be 10-100mg/day orally (5-10mg/day orally or 10-300 mg/day i.v.); and for 'second generation' CCK antagonists, 1-2mg/day (oral) or 0.5-1.5 mg/day (i.v.).

The present invention will now be illustrated by the following non-limiting examples:

Example 1 : Intravenous Emulsions

(a)	L-740,093 (active (a))	0.00025g
	Morphine sulphate (active (b))	0.010g
	Soya bean oil (i)	0.4000ml
	Phosphatidyl choline (emulsifier)	0.0240g
	Pluronic F 68 (surfactant)	0.0040g
	Water (ii)(adjusted to pH 7 to 7.5 and made isotonic with sorbitol q.s.)	2ml

The injection is prepared using aseptic techniques and sterile materials. The MK-329 is dispersed in the soya bean oil and the morphine is dissolved in the water. The two phases are emulsified using standard pharmaceutical technology and stabilised by the phosphatidyl choline and Pluronic F 68. The amount of morphine sulphate may be altered to provide a range of potencies. A 2ml bolus intravenous injection may be administered every four hours, or the formulation may be incorporated into the reservoir of an analgesic self-administration device.

		1g =~ 1ml
(b)	MK-329 (a)	0.0015g
	Fentanyl citrate (b)	0.0024g
	Soya bean oil (i)	0.0993g
	Safflower oil (i)	0.0993g
	Phosphatidyl choline (emulsifier)	0.0125g
	Glycerine	0.0200g

	Water (qs 1 ml) (ii)	0.7665g
	qs 0.1 N NaOH to adjust pH to 7.0 - 7.5	

The ingredients were mixed together and emulsified in a similar manner to that described above in Example 1(a).

Example 2 : Intravenous Infusions

(a)	MK-329 (a)	0.015g
	Morphine sulphate (b)	0.100g
	Cottonseed oil (i)	200ml
	Polysorbate (surfactant)	1.6g
	Fractionated egg phospholipids (emulsifier)	12.000g
	Hydroxypropyl methylcellulose (ii)	5.000g
	Water (ii) (adjusted to pH 7 to 7.5 and made isotonic with sorbitol)	1000ml

The MK-329 is dispersed in the oil phase and the fentanyl citrate is dispersed in the aqueous phase. The emulsion is formed using standard pharmaceutical techniques. One litre of emulsion may be adminstered intravenously over a 24-hour period. The amount of morphine may be adjusted to allow a range of doses, depending on the response of individual patients.

(b)	L-365,260 (a)	0.03g
	Morphine sulphate (b)	200mg
	Soya bean oil (i)	100g
	Egg yolk lecithin (emulsifier)	12g
	Glycerine (i)	25g
	Gelatine (ii)	50 g
	Water q.s. to (ii)	1 litre

All the ingredients are emulsified together, except the gelatine, at 80°C. The temperature is reduced to about 40°C and the gelatine added.

Example 3 : S.R. Suppository

Butorphenol tartrate (b)	30mg
MK-329 (a)	12mg
Hydroxypropyl methylcellulose (ii)	300mg
Aerosil R972* (thickener)	100mg
Witepsol H15 or ((i), glycerides)	
Witepsol W25 to	2500mg

(*Hydrophobic silica)

The MK329 and Aerosil are added to molten Witepsol. The butorphenol is blended with hydroxypropyl methylcellulose and then added to the Witepsol mixture. The mixture is poured into 3 ml moulds and shock cooled to room temperature.

Example 4 : Coated S.R. Tablet

(a) Core

MK-329 (a)	0.015g
Suppocire DM (((i), glyceride*)	0.100g
Levorphanol tartrate (b)	0.006g
Crosslinked polyvinyl pyrrolidone (PVP) (ii)	0.010g
Lactose (ii)	0.175g

Coating

Cellulose acetate	0.020g

(b) Core

Dihydrocodeine tartrate (b)	180mg
Suppocire DM ((i), glyceride)	100mg
L-741,528 (a)	4mg
Polyvinylpyrrolidone (PVP) (ii)	40mg
Lactose (ii)	123mg
Magnesium stearate (lubricant)	1.5mg

* Suppocire DM is a mixture of hemi-synethetic glycerides of C_{12-18} saturated with fatty acids.

Coating

Hydroxypropyl methylcellulose (ii)	14.45mg
Triethyl citrate (plasticiser)	6.9mg
30% aqueous dispersion	
ethyl cellulose	17.21mg
Purified water	q.s.

The dihydrocodeine tartrate is dispersed in molten Suppocire which is cooled with constant stirring to give a granular product. These granules are blended with other materials and tableted.

Example 5 : S.R. Tablet

L-740,093 (a)	0.002g
Suppocire DM ((i), glyceride)	0.100g
Dihydrocodeine tartrate (b)	0.180g
Magnesium stearate (lubricant)	0.003g
Hydroxypropyl methyl cellulose (ii)	0.250g
	0.548g

The L-740,093 is dissolved in molten Witepsol W25 at 50-60°C. The resulting liquid is atomised into a chamber containing chilled nitrogen (gas) at about 10°C. Spherical particles produced thereby are in the range 80-120 µm. These are then blended with the dihydrocodeine tartrate and remaining excipients to produce a powder which is tabletted by standard techniques.

Example 6 : S.R. Capsules

L-369,466 (a)	0.0004g
Morphine sulphate (b)	0.100g
Suppocire DM ((ii), glyceride)	0.200g
Sodium alginate (i)	0.200g

The L-369,466 and morphine are incorporated into molten Witepsol. Granules or spheroids are produced by standard pharmaceutical techniques, then blended with the sodium alginate before filling into capsule shells. The amount of morphine in each capsule, for once daily administration, can be changed within the range 30mg to 150mg.

CLAIMS

1. A pharmaceutical formulation comprising

(a) an opioid-potentiating amount of a CCK antagonist;

(b) an analgesic amount of an opioid; and

(c) a pharmaceutically acceptable biphasic carrier comprising

(i) an organic phase comprising a glyceride derivative; and

(ii) a hydrophilic phase.

2. A pharmaceutical formulation according to claim 1, wherein the organic phase (i) has a solubilising capacity for the CCK antagonist in excess of 5mg per gram of organic phase.

3. A pharmaceutical formulation according to claim 1 or 2, wherein the organic phase comprises an oil selected from soya bean, safflower, sesame, rapeseed, peanut, olive, cotton seed and fish oils, alone or in combination with glycerine and/or a wax selected from full and/or partial triglycerides of fatty acids.

4. A pharmaceutical formulation according to any one of claims 1 to 3, intended for intravenous use, wherein the hydrophilic phase is aqueous and has a viscosity of from 2500-7500cp at 20°C.

5. A pharmaceutical formulation according to any one of claims 1 to 3, intended for use as a solid formulation, wherein the hydrophilic phase is gel forming, incorporates the opioid in the gel and forms a matrix incorporating the CCK antagonist and the glyceride derivative.

6. A pharmaceutical formulation according to any one of the preceding claims wherein the hydrophilic phase comprises a pharmacologically and pharmaceutically acceptable polymer or salt thereof selected from proteins such as gelatine, hyaluronic acid, alginic acids or salts thereof such as sodium alginate, carboxymethylcellulose (optionally cross-linked), methyl cellulose, other cellulose derivatives which are water-swellable such as hydroxypropylmethylcellulose and hydroxyethyl-cellulose or other water-

swellable polymers such as polyvinyl pyrrolidone (PVP) or water-soluble polymers such as lactose.

7. A pharmaceutical formulation according to any one of the preceding claims, wherein the carrier is in the form of an oil-in-water emulsion.

8. A pharmaceutical formulation according to claim 7, wherein the oil-in-water emulsion comprises

(i) an oil phase comprising a glyceride derivative; and

(ii) an aqueous phase optionally comprising a buffer whereby the emulsion has a pH of from 6.5 to 7.5 and optionally comprises an isotonicity regulator whereby the aqueous phase is made isotonic to blood plasma.

9. A pharmaceutical formulation according to claim 7 or 8 wherein the average particle size of the emulsion is from 0.2 to 3.0μm.

10. A pharmaceutical formulation according to any one of claims 7 to 9 further comprising en emulsifying agent, a surfactant and/or a pH adjuster.

11. A pharmaceutical formulation according to any one of the preceding claims, wherein the CCK antagonist (a) has been incorporated into the organic phase (i) and the opioid analgesic (b) has been incorporated into the hydrophilic phase (ii).

12. A pharmaceutical formulation according to any one of the preceding claims, wherein the ratio of component (i) to component (ii) is within the range of 10:1 to 1:5 by weight.

13. A pharmaceutical formulation according to any one of the preceding claims, wherein the ratio of component (a) to component (b) is within the range of 1:2 to 1:40 by weight.

14. A pharmaceutical formulation according to any one of the preceding claims, wherein the CCK antagonist (a) is selected from:

3S-(-)-(1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3R-3-(N′-(3-methylphenyl)ureido)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

N-[1,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N´-[3-(1,2,4-oxodiazol-5-one)phenyl]urea;

(-)-N-[2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N´-[indan-5-yl]urea; and

[N-[(3R)-5-(3-azabi-cyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N´-(3-methylphenyl)urea].

15. A pharmaceutical formulation according to any one of the preceding claims, wherein the opioid (b) is selected from morphine, codeine, or a salt thereof, and 14-hydroxymorphinan opioid analgesics and salts thereof.

16. A pharmaceutical formulation according to any one of the preceding claims as a solid formulation, an injectable emulsion, suppositories or tablets.

17. A pharmaceutical formulation according to any one of the preceding claims in unit dosage form suitable for the delivery of 0.5 to 300mg per day of CCK antagonists to a patient in need thereof.

18. A pharmaceutical formulation according to claim 17 in unit dosage form suitable for oral use or use as a suppository for the delivery of 1 to 100mg per day of CCK antagonist to a patient in need thereof.

19. A pharmaceutical formulation according to claim 17 in unit dosage form suitable for intravenous use for the delivery of 1 to 300 mg per day of CCK antagonist to a patient in need thereof.

20. A method of treating chronic and neuropathic pain comprising administering to a patient in need thereof a pharmaceutical formulation according to any one of the preceding claims.

INTERNATIONAL SEARCH REPORT

Inter. Application No
PCT/GB 98/03076

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/55 A61K9/107 A61K9/20 //(A61K31/55,31:485)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 791 215 A (ROVATI ET AL.) 13 December 1988 cited in the application see column 1, line 1 - line 44 see column 31, line 4 - line 45	1-20
A	GB 1 564 039 A (BERGER) 2 April 1980 see the whole document	1-20
A	EP 0 222 614 A (ELI LILLY AND COMPANY) 20 May 1987 see the whole document	1-20
A	EP 0 391 369 A (YISSUM RES. DEV. COMP. HEBREW UNIVERS. JERUSALEM) 10 October 1990 see page 8; example 2	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 February 1999	16/02/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter[redacted]al application No.
PCT/GB 98/03076

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 20 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter[redacted]l Application No
PCT/GB 98/03076

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